REMARKS/ARGUMENTS

This Amendment and Remarks are in response to the Final Office Action dated November 20, 2006 and filed with a Request for Continued Examination. Reconsideration of this application and entry of this amendment is respectfully requested.

Claims 1-2, 7-11, and 20-28 are pending in this application. Claims 3-6 and 12-17 have been withdrawn as the result of an earlier restriction requirement without prejudice to Applicant's right to pursue the subject matter of the withdrawn claims in one or more related applications. Claims 18-19 were canceled in the response filed July 14, 2006. Claim 29 has been added. Support for claim 29 can be found in the specification at least in paragraph 0037 and in Example 3.

Rejections Under 35 U.S.C. §103

Claims 1-2, 7-11 and 18-20 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. (US Patent Application No. 09/781,124) and Thomson et al. (The Journal of Immunology, 1998, Vol. 160, pages 1717-1723), claim 21 is unpatentable over Hooper et al. in view of Thomson et al. and further in view of Curiel et al., claim 22 is unpatentable over Hooper et al. in view of Thomson et al. and further in view of Rutter et al. and claim 23 is unpatentable over Hooper et al. in view of Thomson et al. and further in view of Newton. Claims 18-19 were canceled in the previous response filed July 14, 2006. Applicants respectfully submit that the Examiner has not established *prima facie* obviousness of claims 1-2, 7-11 and 20 in view of the cited references as is discussed further *infra*.

The Legal Standard

To reject a claim under 35 U.S.C. §103(a), the Examiner bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *In re Bell*, 26 USPQ.2d 1529 (Fed. Cir. 1992). If the Examiner cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *In re Oetiker*, 24 USPQ.2d 1443 (Fed Cir. 1992). The Examiner must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the Examiner must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the application." *In re Kotzab*, 55 USPQ.2d 1316 (Fed. Cir. 2000). Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problems to be solved. *Id.*

Second, the prior art references cited by the Examiner must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *In re Dow Chemical*, 5 USPQ.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *Id.*

Finally, the Examiner must demonstrate that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 USPQ.2d 1769 (Fed. Cir. 2000).

If any one of these three factors is not met, the PTO has failed to establish *prima facie* obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

Claims 1-2, 7-11 and 18-20 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. and Thomson et al. .

1. The Cited References Do Not Teach Each Element of the Claimed Invention

As recited in claim 1, the polyproteins comprise external immunogens of membrane-associated proteins of variola major or immunologically cross-reactive poxviruses. External immunogens and external epitopes are defined in the instant specification in paragraphs 0020 and 0021, respectively. An external epitope is defined as a portion of an external immunogen. Therefore, by definition, the polyprotein of claim 1 comprises more than mere epitopes

Independent claim 8 recites a polyprotein comprising an external immunogen. As stated *supra*, external immunogens comprise more than mere epitopes.

Independent claim 10 recites a polyprotein comprising an external immunogen. As stated *supra*, external immunogens comprise more than mere epitopes.

Independent claim 20 recites an immunogenic composition comprising a complex of polypeptides wherein each polypeptide comprises an external immunogen of a membrane associated protein.

Hooper discloses an immune globulin composition comprising one or more monoclonal antibodies against vaccinia antigens (paragraph 0005) wherein the monoclonal antibodies are neutralizing antibodies. Hooper discloses generating neutralizing antibodies by immunizing with vaccinia antigens. Hooper further discloses the vaccinia gene products L1R and A33R as preferred antigens for generating neutralizing antibodies. Hooper does not teach nor suggest polyproteins or immunogenic compositions comprised of polyproteins.

Thomson discloses delivery of multiple epitope DNA vaccines for the induction of cytotoxic T lymphocyte (CTL) responses. Thomson discloses DNA vaccines comprising "polytopes" which Thomson defines as comprising a series of minimal CTL epitopes, the DNA encoding the epitopes comprising only the epitope sequence and not any other portion of the gene of interest (page 171, column 2, first paragraph continued from column 1). Furthermore, Figure 1B of Thomson depicts the amino acid sequence of a polytope, which is described in the figure legend as "10 contiguous CD8 epitopes". As depicted in Figure 1B, none of the amino acid sequences encoding for an epitope includes more than ten amino acids. Thomson does not teach or suggest polyproteins, particularly polyproteins comprising more than mere epitope sequences. Furthermore, Thomson discloses epitope-based CTL vaccines only for EBV, HIV and certain cancers, and does not disclose vaccines for smallpox.

Applicants respectfully assert that the combination of Hooper and Thomson do not render the pending claims *prima facie* obvious. In order to render the pending claims *prima facie* obvious, a combination of the two references must teach or suggest

a polyprotein comprising more than mere epitope sequences from at least one membrane associated protein. Hooper teaches complete proteins, but does not teach external immunogens, and Thomson teaches sequences limited to just the minimal epitope-encoding amino acids (less that 10 amino acids). All the pending claims recite polyproteins comprising amino acid or nucleic acid sequences encoding for more than mere epitopes. These two references, taken together, do not teach or suggest a polyprotein combining multiple proteins having sequences longer than epitopes.

2. The Prior Art References Must Suggest That The Invention Would Have a Reasonable Expectation of Success

Combining the teachings of Hooper with the teachings of Thomson would not allow a person of ordinary skill in the art to create the polyprotein of the instant application with a reasonable expectation of success. Hooper teaches that certain proteins from vaccinia virus can induce neutralizing antibodies. Thomson teaches that epitope-based CTL vaccines may be effective against EBV, HIV and certain cancers. Thomson specifically states that multiple epitopes are required to generate CTL responses. It is well known to a person of ordinary skill in the art that neutralizing antibodies are induced by surface or secreted antigens and CTL responses are induced by antigens which have been processed, degraded and associated with self class I MHC molecules. Moreover, whereas CTL recognize epitopes removed from their native context and in the context of MHC molecules, neutralizing antibodies generally recognize epitopes that have at least some dependence on the native folding and sequence context of the parent antigen. These features are obviously not preserved in a head-to-tail array of epitopes as taught by Thomson. Thus, while Thomson's approach can work for CTL epitopes, it is expected not to work for antibody epitopes. Therefore there is no expectation of success to combine teachings for generating neutralizing antibodies to vaccinia-associated proteins with teachings of epitope-based CTL vaccines to yield polyprotein-based immunogenic compositions vaccines for poxviruses.

In view of the foregoing, Applicants respectfully submit that the combination of Hooper et al. and Thomson et al., would not suggest to one of ordinary skill in the art

that a polyprotein comprising external immunogens or complete proteins of membrane-associated proteins of variola major or immunologically cross-reactive poxviruses would have a reasonable expectation of success.

3. The Prior Art References Must Provide Motivation, Suggestion, or Teaching of the Desirability of Making the Specific Combination Made by the Applicant.

A person or ordinary skill would not seek to combine the teachings of Thomson, specifically epitope-based CTL vaccines to EBV, HIV or cancer, with the teachings of Hooper, namely methods for production of neutralizing antibodies to vaccinia antigens, to generate a polyprotein-based immunogenic composition comprising external immunogens or complete proteins of membrane-associated proteins of variola major or immunologically cross-reactive poxviruses.

The Examiner must present a clear and particular showing (not a casual unsupported assertion) that a person having ordinary skill in the art would have been motivated to combine the cited references. See C.R. Bard, Inc. v. M3 Sys., Inc. 157 F.3d 1340, 1352, 48 USPQ.2d (BNA) 1225, 1232 (Fed. Cir. 1998). Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." *In re Dembiczak*, 50 USPQ.2d. 1614 (Dec. 1999).

In the present action, the Examiner has failed to meet this burden and thus shifts the burden to the Applicants. Therefore, no legal showing of obviousness can be considered to be pending in the present case.

Based on the foregoing, Applicant respectfully submits that Hooper and Thomson, either singly or in combination, do not teach or suggest each and every element of claims 1-2, 7-11 and 20, there would be no reasonable expectation of success to generate the presently claimed invention based on the combination of Hooper and Thomson and there is no motivation or suggestion to combine the references. Therefore the Examiner has not established *prima facie* obviousness of claims 1-2, 7-11 and 20 based on Hooper and Thomson. Accordingly, Applicant respectfully submits that claims 1-2, 7-11 and 20 and are not obvious under 35 USC

§103(a) over the cited prior art and request the withdrawal of the outstanding rejection on this basis.

Claim 21 stands rejected under 35 USC §103(a) as being unpatentable over Hooper et al. in view of Thomson et al. as applied to claims 1-2, 7-11 and 18-20, and further in view of Curiel et al.

It has been determined *supra* that claim 20 is not *prima facie* obvious over Hooper in view of Thomson because these references do not teach or suggest each and every element of independent claim 20, there is not a reasonable expectation of success from combining these references and there is no motivation or suggestion to combine them.

The deficiencies of Hooper and Thomson as invalidating 35 U.S.C. §103(a) art are not remedied by Curiel. Curiel teaches viral conjugates wherein the virus and a nucleic acid binding domain are bound by a biotin-streptavidin bridge.

The combination of Hooper, Thomson and Curiel do not teach or suggest all the elements of claim 21, specifically immunogenic compositions comprised of complexes of polypeptides wherein each polypeptide comprises an external immunogen of a membrane-associated protein of variola major or immunologically cross-reactive poxviruses wherein the polypeptides are biotinylated and the complex is formed by the additional of avidin or streptavidin.

Therefore Applicant respectfully submits that the cited references, either singly or in combination, do not teach or suggest each and every element of claim 21 and therefore the Examiner has not established *prima facie* obviousness of claim 21 based on Hooper in view of Thomson and Curiel.

Claim 22 stands rejected under 35 U.S.C. §103(a) as unpatentable over Hooper in view of Thomson and in further view of Rutter et al.

Claim 22 is not *prima facie* obvious over Hooper in view of Thomson as discussed supra for claims 1-2, 7-11 and 20 because these references do not teach or suggest each and every element of claim 22, there is not a reasonable expectation of

success to generate the presently claimed invention based on the combination of these references, and, as a result, there is no motivation to combine them.

The deficiencies of Hooper and Thomson are not remedied by Rutter. Rutter discloses agents to facilitate the delivery of a viral subunit vaccine wherein the agent is a liposome.

The combination of Hooper, Thomson and Rutter does not teach or suggest all the elements of claim 22, specifically immunogenic compositions comprised of complexes of polypeptides wherein each polypeptide comprises an external immunogen of a membrane-associated protein of variola major or immunologically cross-reactive poxviruses when the complex is formed by anchoring the polypeptides in a liposome or micelle.

Therefore Applicants respectfully submit that the cited references, either singly or in combination, do not teach or suggest each and every element of claim 22 and therefore the Examiner has not and cannot establish *prima facie* obviousness of claim 22 based on Hooper in view of Thomson and Rutter.

Claims 23-26 rejected under 35 U.S.C. §103(a) as unpatentable over Hooper in view of Thomson and further in view of Newton et al.

Claims 23-26 are not *prima facie* obvious over Hooper in view of Thomson as discussed *supra* for claims 1-2, 7-11 and 20 because these references do not teach or suggest each and every element of claims 23-26, there is not a reasonable expectation of success to generate the presently claimed invention based on the combination of these references, and, as a result and there is no motivation to combine them.

The deficiencies of Hooper and Thomson are not remedied by Newton. Newton discloses linkers to link peptides wherein the linkers include a $(GGGGS)_3$ linker. Newton also teaches affinity tags.

The combination of Hooper, Thomson and Newton does not teach or suggest all the elements of independent claim 23, specifically a polyprotein comprising external immunogens of membrane-associated proteins of variola major or immunologically

cross-reactive poxviruses wherein the individual proteins are jointed through a linker-spacer peptide. Therefore Applicant respectfully submits that the cited references, either singly or in combination, do not teach or suggest each and every element of claims 23-26 and therefore the Examiner has not established *prima facie* obviousness of claims 23-26 over Hooper in view of Thomson and Newton.

In view of the foregoing, Applicant respectfully submits that none of Hooper, Thomson, Curiel, Rutter or Newton, either alone or in combination, teach or suggest polyproteins comprising external immunogens of membrane-associated proteins of variola major or immunologically cross-reactive poxviruses or immunogenic compositions comprising such polyproteins. Furthermore, there is no expectation of success nor motivation or suggestion to combine Hooper and Thomson. Therefore Applicants respectfully submit that the Examiner cannot establish *prima facie* obviousness of claims 1-2, 7-11 and 20-23. Accordingly, Applicant respectfully submits that claims 1-2, 7-11 and 20-23 are not obvious under 35 USC §103(a) over the cited prior art and requests the withdrawal of the outstanding rejections on this basis.

Conclusion

Applicants respectfully assert that the presently pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 1/26/07

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